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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/160,067	09/24/1998	WALTER H. GUNZBURG	GSF98-04A	5908

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/160,067	GUNZBURG ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 11/28/03 has been acknowledged.
Claims 1-4 and 6-22 are pending, and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). Each amendment document that includes a change to an existing claim, or submission of a new claim, must include a complete listing of all claims in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.

*The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/28/03 has been entered.

Double Patenting

Claims 1-4 and 6-22 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being un-patentable over claims 1-24 of US 6,540,995 (Application No. 09/442,979), for the same reasons of record as set forth in the office action mailed on 11/18/02. In response the filed on 11/28/03 the applicant states that applicant will address the rejection upon an indication that there is allowable subject matter in the referenced files.

Claim Rejections - 35 USC § 103

Claims 1-4, 6-9, 15-19 and 21-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over of Tai et al (FASEB Journal 7: 1061-1069, 1993) and Merten et al. (Cytotechnology 7(2): Abstract, 1991) in view of Wei et al. (Human Gene Therapy 5: 969-978, 1994) for the same reasons of record as set forth in the office action mailed on 11/18/02.

The instant invention is drawn to a capsule comprising a porous membrane, which encapsulates cells expressing cytochrome P450 gene, wherein the membrane is permeable to prodrug molecule but cytochrome p450 expressed by the gene is retained within the capsule.

Response to arguments

The applicant argues that the cited art does not teach or suggest encapsulation of cells, which produce a non-secreted protein. The applicant argues that cytochrome P450 is a membrane-bound enzyme and is not a secreted protein. The applicant argues that when Merten refers to retention of a product produced in a capsule, it is in the context of a mammalian cell culture system in which the retained product is harvested from the capsules, not in the context of delivering the expressed product of a gene in vivo. The applicant further argues that a person of skill in the art would not be motivated to encapsulate the genetically engineered mouse fibroblasts that produce cytochrome

P450, a membrane-bound enzyme to convert a chemotherapeutic prodrug into its active state because the cytochrome P450 would be unable to leave the capsule. The applicant further argues that the cited art teaches away from manipulating the pore size of the capsule to allow entry of components outside the capsule into the capsule. The applicant argues that the prior art combination of record has been made with the advantage of impermissible hindsight and the suggestion or motivation for combining the references and expectation of success are not found in the prior art but in the applicant's disclosure (response 11/28/03, pages 3-5).

However, this is found NOT persuasive because the scope of invention as claimed is not limited to membrane-bound cytochrome P450 but to the retention of cytochrome 450 expressed by cells inside the capsule. Mertin clearly teaches an encapsulation method which result in the retention of cellular products while allowing the survival of encapsulated cells by infusion of growth media by selective molecular weight cutoff control (Mertin page 123-125, table 1-2, especially page 128, col.2, para. 3). Therefore encapsulation system as taught by Mertin clearly teaches an encapsulated bioreactor wherein the product produced by the encapsulated cells is retained within the capsule while allowing growth media in, which is comparable to the invention as claimed. Similarly Tai teaches that appropriate semi-permeability is required to allow easy diffusion of secreted gene product without compromising the immunoisolating properties of the membrane (Tai page 1061, col.2). Tai further teaches the control of membrane permeability by adjusting sodium alignate and poly-l-lysine concentration (page 1062, fig-1; page 1063, fig-2, fig-3). Therefore Mertin and Tai clearly suggested the manipulation of membrane permeability that not only promotes survival of encapsulated cells but control the diffusion of cellular and extra-cellular products. Thus considering the combined teaching (not the impermissible hindsight as argued by applicant) one ordinary skill in the art would have clearly motivated to manipulate the pore size of the capsule, which allows entry of components outside the capsule into the capsule while retaining the cellular products. Since one ordinary skill in the art would be able to able to manipulate the selective permeability of the capsule membrane, which retains the cytochrome 450 expressed by cells while allowing prodrug

molecules to diffuse in, it is eminent that prodrug would convert into an active state in the capsule micro environment.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In instant case it is not improper hindsight reasoning but Mertin and Tai who clearly suggested the manipulation of membrane permeability that not only promotes survival of encapsulated cells but control the diffusion of cellular and extra-capsular products.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, considering the combined teaching one ordinary skill in the art would be able to manipulate the selective permeability of the capsule membrane, which retains the cytochrome 450 expressed by cells while allowing prodrug molecules to diffuse in.

Thus, it would have been obvious to one ordinary skill in the art at the time of filing, to modify the teaching of Tai and Merten who teaches the encapsulation of genetically engineered cells with selected membrane permeability, with the teaching of Wei who teaches genetically engineered cells that produces p450 which activates an inert prodrug. One would have been motivated to encapsulate the cytochrome p450 producing cells in order to retain the P450 gene product within the capsule (Marten) or to avoid immune rejection (Tai). One would have a reasonable expectation of success

because prior art clearly teaches that manipulation of pore size of capsule membrane is well within the reach of one ordinary skill in the art (see Merten, page 128, col.2 para 3). Thus, invention as claimed is prima facie obvious in view of combined teaching of cited art of record.

Conclusion

No claims are allowed.

This is a RCE of applicant's earlier Application No. 09/160,067. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel Ph.D. can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

S. Kaushal
PATENT EXAMINER

JEFFREY FREDMAN
PRIMARY EXAMINER